Hemotherapy in Suspected Dermatomyositis

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OPPORTUNITIES TO EVALUATE therapy in a disease as rare as dermatomyositis are infrequent. Apparent benefit from a new form of treatment, the intramuscular administration of concentrated leukocyte suspensions, in a patient with dermatomyositis unresponsive to all conventional therapy is reported here in the hope that further trial in other patients will define the value of this therapeutic approach.

Present therapy in dermatomyositis is unsatisfactory. Before the advent of corticotropin (ACTH) and cortisone, benefit was obtained in an occasional case with the use of testosterone and tocopherols. Cortisone and related steroids have proved a mixed blessing, since the control of acute inflammatory manifestations is often counterbalanced by serious hazards attendant on prolonged administration.[2] Not every patient with a collagen disease will respond to steroids, and the incidence of refractoriness rises with increasing duration of therapy.

Kurnick[7] recently described a new therapy for systemic lupus erythematosus, consisting of the intramuscular administration of leukocytes, either in whole blood or in concentrated suspension. The rationale of this therapy is of considerable interest. The "L.E." phenomenon involves ingestion by a polymorphonuclear leukocyte of a nuclear mass (from another leukocyte) which has been rendered structureless by depolymerization of desoxyribosenucleic acid (DNA). Depolymerization of DNA is accomplished by an enzyme, DNase, which is present in serum and probably in all cells. DNase is normally held in check by an inhibitor present in leukocytes. Destruction of DNase inhibitor permits the L.E. phenomenon to take place. This destruction is thought to be due to a serum factor (possibly plasmin) which gains entry to the cell with the aid of the specific L.E. gamma globulin described by Haserick and co-workers.[4]

A second function of the injected leukocytes has been described.[7] The specific L.E. gamma globulin described by Haserick[4] is thought to be an antibody against mesenchymal cell membranes, and the stroma of the injected leukocytes, which are of mesenchymal origin, may serve a therapeutic purpose by adsorbing the circulating abnormal globulin. Increased concentrations of gamma globulin are found with regularity in every collagen disease, and these proteins may (in a manner similar to that of L.E. gamma globulin) participate in the genesis of the disease with which they are associated.

The intramuscular administration of 30 cc. of compatible blood from a normal donor will supply the recipient with 150 to 300 million leukocytes. Separation of leukocytes from blood makes it possible to give a dose of 500 million leukocytes in a volume of approximately 5 cc.

Success with hemotherapy has been described in systemic lupus erythematosus, even in steroid-resistant cases,[7] but its usefulness in other collagen diseases has not been assessed. The sequence of events in the following case suggests that hemotherapy may be effective in dermatomyositis.

REPORT OF A CASE

A 30-year-old Caucasian housewife had had recurrent epistaxis since the age of four years and irregular and profuse menstrual bleeding since menarche at age 13. At the age of 14 bleeding of the gums, petechiae and multiple ecchymoses developed. When the patient was examined in 1940 at the University of California Medical Center, San Francisco, hemoglobin content was 9.8 gm. per 100 cc. of blood and erythrocytes numbered 3.6 million per cu. mm. Leukocytes numbered 3,800 per cu. mm. and platelets 60,000 per cu. mm. The sedimentation rate was 22 mm. in one hour, the icteric index 5 units, prothrombin concentration 100 per cent, clot retraction index 29, bleeding time 30 minutes, and clotting time (Lee White) 9 minutes. A capillary fragility test with a blood pressure cuff inflated to 200 mm. of mercury was positive (50 petechiae). The patient was treated conservatively and was discharged in two weeks.

Two years later, in 1942, appendectomy and removal of an ovarian cyst were carried out. The patient then had recurrence of epistaxis, petechiae, ecchymoses and heavy vaginal bleeding. She was readmitted to the hospital in January, 1943, and at that time the hemoglobin was 8 gm. per 100 cc., erythrocytes 2.8 million per cu. mm., and leukocytes 6,000 per cu. mm. The clotting time was 10 minutes and the bleeding time was over 30 minutes. Pro-

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thrombin concentration was 100 per cent. Platelets numbered 67,000 per cu. mm. of blood.

On February 3, 1943, splenectomy was done. The spleen was slightly enlarged (220 grams) and had three small accessory spleens at the pedicle. There was overgrowth and frequency of germinal centers, the sinuses tended to be empty, and the lining cells were prominent. The microscopic diagnosis was: "Spleen compatible with thrombocytopenic purpura."

At the time the patient was discharged two weeks after operation, the bleeding, clotting and prothrombin times were normal and platelets numbered 200,000 per cu. mm.

In September, 1949, the patient was admitted to Mercy Hospital, Bakersfield, because of recurrent menorrhagia. Dilatation and curettage were done and hypertrophic endometritis was noted. The patient was discharged but was readmitted to the hospital three days later with complaint of fever, headache, backache and pelvic pain.

Upon physical examination, stiffness of the neck and back and tenderness in the left adnexa were noted. A neurologic consultant noted right lower facial weakness, tendon reflexes sluggish in the upper extremities and absent in the lower extremities, and abdominal reflexes absent. Lumbar puncture was carried out. The pressure was above the normal range. The fluid was clear. It contained 10 mg. of protein per 100 cc. and 5 leukocytes per cu. mm. A coccidioidin skin test was strongly positive (a 3 by 4 cm. area of erythema and induration at 48 hours).

The patient had diarrhea on the second day in hospital but recovery thereafter was uneventful and she was discharged in two weeks. The final diagnosis was probable encephalitis, type undetermined.

The patient was readmitted to Mercy Hospital in Bakersfield in December, 1953, for dilatation and curettage because of prolonged vaginal bleeding. The pathologic report again was: "Hypertrophic endometrium."

In January, 1954, the patient noticed blanching of the fingers on exposure to cold, with occasional digital cyanosis and numbness. She was unable to tolerate tolazoline (Priscoline) by mouth and refused sympathectomy.

She was admitted to Santa Barbara Cottage Hospital November 28, 1954, ten months after the onset of Raynaud's phenomenon, with pain and swelling in the right arm of three weeks' duration. Upon examination edema and cyanosis of the entire right upper extremity were noted. A thrombus was palpated in the brachial and axillary vein. The body temperature was 102.2° F. The hemoglobin content was 9.3 gm. per 100 cc. of blood. Erythrocytes numbered 3.2 million per cu. mm. and leukocytes 12,200 per cu. mm. The results of urinalysis were within normal limits. Hot packs were applied to the arm and heparin was administered. The patient was dismissed in two weeks. During this episode there was transitory recurrence of thrombocytopenia, the platelet content falling to 78,000 per cu. mm., but a normal number of platelets was present at the time of discharge. Mild lymphedema and residual tenderness persisted in the right arm.

During the last six months of 1954 typical rheumatoid arthritis developed in the hands and knees. There was satisfactory response to small doses of prednisone.

In February, 1955, the patient noted a subcutaneous lump 2 cm. in diameter in the left upper quadrant of the abdominal wall. It was soft, tender, and of violaceous hue. Biopsy was done in October, 1955, and the histologic sections were examined by three pathologists. Three different diagnoses were given: Focal scleroderma, rheumatoid nodule, chronic arteritis.

The patient was admitted again to Santa Barbara Cottage Hospital April 21, 1956, with complaint of fever and pain in the chest and arms. The illness had begun two days earlier with pain in the muscles of the neck and a temperature of 101° F. There was rapid spread of pain from the neck through the shoulders and arms, and within a short time muscular pain was generalized throughout the body. Use of the muscles intensified the pain and the patient was unable to stand, to take a deep breath or to swallow, because of pain.

When examined, the patient was lying limply in bed, avoiding the slightest motion. The blood pressure was 150/95 mm. of mercury, the temperature 101.6° F., the pulse rate 108 and respirations 20 per minute and somewhat shallow. No abnormalities were noted in the head and neck except for many enlarged tender lymph nodes in the anterior and posterior cervical chains. There was diffuse and exquisite tenderness of all skeletal muscles—so acute that severe pain was elicited by simple passive motion of any of the extremities.

Infectious mononucleosis was suspected, but the heterophil agglutination titer was 1:28 on two determinations during the first week. The patient said she had not eaten undercooked pork. At the time of admission the hemoglobin was 12.3 gm. per 100 cc. of blood. Erythrocytes numbered 4.3 million per cu. mm. and leukocytes 22,500 per cu. mm.—with 58 per cent segmented neutrophils, 13 per cent banded forms and 29 per cent lymphocytes. The sedimentation rate (Westergren) was 74 mm. in one hour. The antistreptolysin titer was 125 Todd units. Urinary excretion of creatine was 193 mg. in 24 hours. The result of an L.E. cell test was negative, as it had been in February, 1956. No pathogenic organisms grew on a culture of blood. The serum transaminase was 110 units (normal 10 to 40 units). Although a biopsy from the left gastrocnemius muscle was negative and creatinuria had not been established, a diagnosis of dermatomyositis was made on the basis of the clinical features and the elevated serum transaminase. Response to therapy with salicylates and small doses of prednisolone was fair. The serum transaminase decreased to 44 units. On the eleventh hospital day the patient was discharged.

Although the patient was confined to a wheelchair, muscular pain became more severe during

the first week at home and prednisolone dosage was increased to 30 mg. per day. The patient had little relief, and testosterone and tocopherols were added to the therapeutic regimen. She remained incapacitated with diffuse muscle pain, tenderness and cramping for the next six weeks. Urinary excretion of creatine rose to 1750 mg. per 24 hours on June 25, supporting the diagnosis of dermatomyositis.

The patient entered Santa Barbara Cottage Hospital for the third time July 3, 1956, with a carbuncle on the left buttock, which was surgically drained. During the week following this minor operation, inflammation of the muscles progressed at an accelerated rate until the patient was again completely immobilized by pain. Urinary creatine excretion (Folin method) was 1670 mg. per 24 hours and by the Taussky[9] method it was 7000 mg. per 24 hours. Prednisone dosage was increased by steps to 90 mg. per day, with only slight relief of pain and no appreciable effect on the profound muscular weakness.

Atrophy of the interosseous muscles of the hands became visible, and serial measurements of the circumference of the extremities gave additional evidence of loss of muscle mass. Dermal involvement was mild, consisting of pruritic irregular erythema and edema of the face, neck and anterior chest lasting one week. After six days of high dosage prednisone therapy, mental hyperactivity and emotional lability were severe enough to suggest impending psychosis, whereupon the dosage of prednisone was decreased to 60 mg. per day. Testosterone and tocopherols had been given continuously, with no apparent benefit. The patient was bedridden and unable to feed herself.

Therapy with leukocyte concentrate was begun July 30, in a dosage of 500 million white blood cells intramuscularly three times weekly. Concomitantly, prednisone was gradually withdrawn. Subjective subsidence of pain occurred within a week, but objective improvement did not occur until the tenth day, after the fourth dose of leukocyte concentrate. At this point there was a rather abrupt decrease in muscular tenderness. For the first time manual compression of extremity muscles did not evoke pain. Improvement was rapid thereafter. The patient began to move about in bed more freely, resumed feeding herself and was able to walk three weeks after the change in therapy.

During the third week of hemotherapy a carbuncle appeared on the posterior aspect of the right shoulder. Response to several antibiotics was indolent, but administration of 30 cc. of gamma globulin was followed by rapid improvement.

The patient was dismissed on the fifty-first hospital day, and hemotherapy was continued on an outpatient basis thrice weekly. During the next six months, injections of leukocyte concentrate were gradually reduced and were discontinued in January, 1957. Urinary creatine excretion was within normal limits (less than 400 mg. per 24 hours) after October, 1956, and in November the patient returned to full duty as a housewife.

Approximately two months following discharge from the hospital, there was a recurrence of rheumatoid arthritis, with mild pain, swelling and stiffness involving the fingers, wrists and elbows. This was not accompanied by any exacerbation of polymyositis, and creatine excretion continued a downward trend. Chloroquine by mouth, 250 mg. three times daily, brought the arthritis under control. Raynaud's phenomenon was still a troublesome symptom at the time of this report.

DISCUSSION

It would seem reasonable to believe that the many unusual events in this patient's medical history are related phenomena, and that thrombocytopenic purpura, encephalitis, rheumatoid arthritis, Raynaud's phenomenon, axillary thrombophlebitis and dermatomyositis were various manifestations of what may be termed a "collagen disease diathesis." Kampmeier[5] emphasized that more than one collagen disease may occur in the same patient, sometimes concurrently. Brunson's recent studies[1] showed that lesions characteristic of several different collagen diseases can be induced simultaneously in a single animal. Nevertheless, Klemperer, who originally promoted the concept of collagen disease, stressed the desirability of making a specific diagnosis of a distinct collagen disease whenever possible.[6]

From a diagnostic standpoint the serum glutamic oxalo-acetic transaminase (aminopherase) determination in this case was uniquely valuable in that it gave support to the clinical diagnosis of dermatomyositis at a time when the urinary creatine excretion and muscle biopsy were still within normal limits. Other investigators[8] have described the diagnostic value of serum transaminase determinations in dermatomyositis.

It is noteworthy that rheumatoid arthritis in the case here presented, flared during convalescence from dermatomyositis and was not prevented by the hemotherapy that was being administered. Use of chloroquine for control of arthritis was prompted by a desire to avoid a return to steroid therapy, and was suggested by the good results reported by Dubois[3] in the treatment of systemic lupus erythematosus with various antimalarial drugs.

Although a disturbance of DNA or DNase does not occur in dermatomyositis, it is of interest that the serum DNase activity of the patient in the present case showed, during treatment, the same downward trend noted in patients with lupus erythematosus who respond to hemotherapy. The serum DNase was 65 ($X10^{-4}$ units per ml.) in July (before therapy), 52 in August, and 28 in December.*

Recovery in this case of steroid-resistant dermatomyositis cannot with certainty be attributed to hemotherapy, since spontaneous remissions occur in dermatomyositis as they do in any collagen disease. Wider evaluation of hemotherapy in the collagen diseases would appear desirable, since steroid resistance is an increasingly frequent problem.

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*DNase determinations courtesy of Dr. N. B. Kurnick.

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Diffuse Cavernous Hemangioma of the Rectum and Rectosigmoid

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CAVERNOUS HEMANGIOMA of the rectum and rectosigmoid is a rare condition. This presentation is concerned with the diffuse expansive type, single contiguous according to the classification of Gentry.[7] In the forty cases reported[1,2,4,6,7,10,12,13] it seems any or all layers of the bowel may be involved.

The commonest symptom in all cases is bleeding. Bleeding is intermittent and may occur in varying degrees of severity in the same person—from bloody spotting or staining with stools to massive hemorrhage. It is important to note that the history of bleeding usually goes back to childhood. Diagnosis may be simply made, as a rule, with the sigmoidoscope, through which may be seen dilated bluish veins beneath a beefy red mucosa. Single or multiple phleboliths seen in a barium enema x-ray study may suggest the presence of the condition. Sections of the lesion usually consist of dilated blood vessel spaces of variable size and shape, lined by endothelium with little fibrous connective tissue. In the case reported herein, the early sigmoidoscopic and x-ray evidence was not sharp and clear, although in retrospect certain clinical observations, noted in writing, should have received more attention.

Since the number of reported cases is small and the majority of patients were treated in the days before the use of antibiotics and before our present day knowledge of the use of blood and electrolytes, very few were reported cured; and some of the early treatment such as irradiation and cauterization appears bizarre now. Kausch[11] reported a case in which the patient was considered cured after a five-stage surgical procedure. Hunt[9] carried out a staged abdominoperineal resection of rectum and rectosigmoid. In the case reported by Bancroft,[2] and later brought up to date by Jaques[10] the superior hemorrhoidal vein was ligated, then was injected distally with sodium salicylate and a colostomy established. Twenty years later an abdominoperineal resection was done for continuing symptoms and complications.

The following is the fortieth case reported of diffuse, expansive[7] cavernous hemangioma of the rectum and rectosigmoid. It will be seen from the nature of the present case that this condition may well be a trap for the unwary.

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REPORT OF A CASE

A white man, 37 years of age was first observed March 10, 1952, with principal complaint of anorectal pain and bleeding with bowel movements, intermittent since early childhood. The pain was burning and cutting in character, was experienced with bowel movements only and had become very severe during the preceding month. The bleeding which occurred during bowel movements was sufficient to drip and run into the bowl. Protrusions had been present before hemorrhoidectomy that was done in 1946. The patient said bleeding had never stopped since that operation. The physician had discharged him about a month after the operation, stating he could not find the cause of the bleeding.

Upon proctologic examination it was noted that the perianal skin was edematous, weeping and excoriated, with large folds. A small fibrotic nodule (which probably had developed from hemorrhoidectomy) was observed both anteriorly and posteriorly in the perianal skin. On digital examination the sphincter was noted to be in moderate spasm. There was no tenderness and no masses. Upon anoscopic examination, considerable postoperative scar tissue in the anal canal and a large hemorrhagic anterior internal hemorrhoid actively oozing venous blood were observed. The mucous membrane of the distal rectal ampulla was rather redundant. Sigmoidoscopic examination was unsuccessful because of inadequate preparation, but even without it the situation seemed rather obvious and arrangements were made for hemorrhoidectomy.

On the day of operation, erythrocytes numbered 4.44 million per cu. mm. of blood and the hemoglobin content was 13.6 gm. per 100 cc. The differential count of leukocytes was within normal limits.

Caudal anesthesia was administered and sigmoidoscopic examination to 25 cm. above the anus was